10796673 ✓

~~09852850.1~~

8/12/04

1624

Welcome to STN International! Enter x:x

LOGINID:ssspta1611sxp

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	Feb 24	PCTGEN now available on STN
NEWS 4	Feb 24	TEMA now available on STN
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NEWS 10	Apr 11	Display formats in DGENE enhanced
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NEWS 12	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 13	Jun 13	Indexing from 1947 to 1956 added to records in CA/CAPLUS
NEWS 14	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 15	Apr 28	RDISCLOSURE now available on STN
NEWS 16	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
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NEWS 18	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 19	May 19	Simultaneous left and right truncation added to WSCA
NEWS 20	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation
NEWS 21	Jun 06	Simultaneous left and right truncation added to CBNB
NEWS 22	Jun 06	PASCAL enhanced with additional data
NEWS 23	Jun 20	2003 edition of the FSTA Thesaurus is now available
NEWS 24	Jun 25	HSDB has been reloaded
NEWS 25	Jul 16	Data from 1960-1976 added to RDISCLOSURE
NEWS 26	Jul 21	Identification of STN records implemented
NEWS 27	Jul 21	Polymer class term count added to REGISTRY
NEWS 28	Jul 22	INPADOC: Basic index (/BI) enhanced; Simultaneous Left and Right Truncation available

NEWS EXPRESS	April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

Patel <7/28/2003>

* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:42:41 ON 28 JUL 2003

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 09:42:46 ON 28 JUL 2003
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 25 JUL 2003 HIGHEST RN 555152-78-8
DICTIONARY FILE UPDATES: 25 JUL 2003 HIGHEST RN 555152-78-8

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

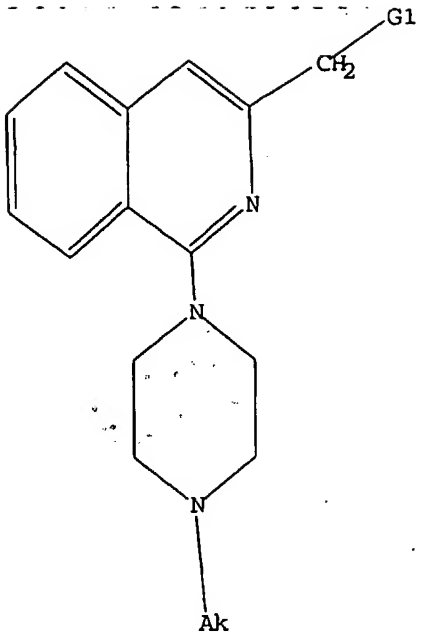
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09852850.1

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



G1 Cb,Cy,Hy

Structure attributes must be viewed using STN Express query preparation.

=> s l1 sss full
FULL SEARCH INITIATED 09:43:17 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 1033 TO ITERATE

100.0% PROCESSED 1033 ITERATIONS 10 ANSWERS
SEARCH TIME: 00.00.01

L2 10 SEA SSS FUL L1

=> file caold

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	148.15	148.36

FILE 'CAOLD' ENTERED AT 09:43:23 ON 28 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGIstRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> s l1
REGIstRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

SAMPLE SEARCH INITIATED 09:43:28 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 66 TO ITERATE

100.0% PROCESSED 66 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 833 TO 1807
PROJECTED ANSWERS: 0 TO 0

L3 0 SEA SSS SAM L1

L4 0 L3

=> s l2
L5 0 L2

=> file caold
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 0.80 149.96

FILE 'CAOLD' ENTERED AT 09:44:30 ON 28 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGIstRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

```
=> s l1 sss full
   REGIstRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.



FULL SEARCH INITIATED 09:44:50 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   1033 TO ITERATE

100.0% PROCESSED   1033 ITERATIONS                          10 ANSWERS
SEARCH TIME: 00.00.01

L6            10 SEA SSS FUL L1



L7            0 L6

=> logy
LOGY IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> log y
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               0.40     298.91

STN INTERNATIONAL LOGOFF AT 09:45:06 ON 28 JUL 2003
```

Welcome to STN International! Enter x:x

LOGINID:ssspta1611sxp

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

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NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

Patel <7/28/2003>

* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:38:26 ON 28 JUL 2003

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 09:38:37 ON 28 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 25 JUL 2003 HIGHEST RN 555152-78-8
DICTIONARY FILE UPDATES: 25 JUL 2003 HIGHEST RN 555152-78-8

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

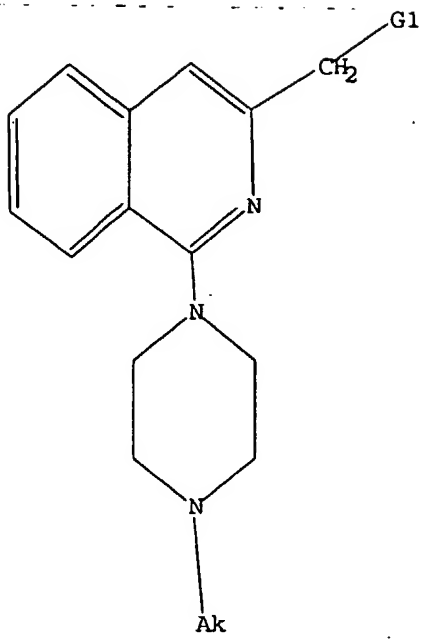
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09852850.1

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



G1 Cb,Cy,Hy

Structure attributes must be viewed using STN Express query preparation.

```
=> s l1
SAMPLE SEARCH INITIATED 09:38:59 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     66 TO ITERATE

100.0% PROCESSED      66 ITERATIONS                              0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          833 TO     1807
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 09:39:06 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   1033 TO ITERATE

100.0% PROCESSED    1033 ITERATIONS                             10 ANSWERS
SEARCH TIME: 00.00.01

L3           10 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                             148.15     148.36
```

FILE 'CAPLUS' ENTERED AT 09:39:15 ON 28 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 28 Jul 2003 VOL 139 ISS 5
FILE LAST UPDATED: 27 Jul 2003 (20030727/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 4 L3

=> d l4 fbib hitstr abs total

L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:244638 CAPLUS
DN 130:311813
TI Preparation of piperazinylisoquinolines and analogs as serotonin antagonists
IN Ueno, Kohshi; Sasaki, Atsushi; Kawano, Koki; Okabe, Tadashi; Kitazawa, Noritaka; Takahashi, Keiko; Yamamoto, Noboru; Suzuki, Yuichi; Matsunaga, Manabu; Kubota, Atsuhiko
PA Eisai Co., Ltd., Japan
SO PCT Int. Appl., 740 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9918077	A1	19990415	WO 1998-JP4465	19981002
W: US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
			JP 1997-284290 A	19971002
JP 2000053647	A2	20000222	JP 1998-281752	19981002
			JP 1997-284290 A	19971002
			JP 1998-153416 A	19980602
EP 1020445	A1	20000719	EP 1998-945593	19981002
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
			JP 1997-284290 A	19971002
			WO 1998-JP4465 W	19981002
US 6340759	B1	20020122	US 2000-509778	20000331

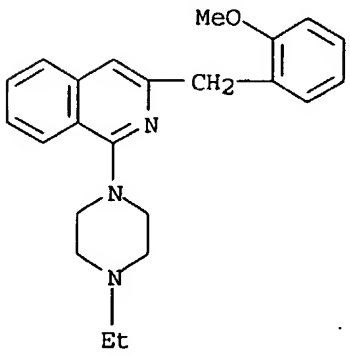
JP 1997-284290 A 19971002
WO 1998-JP4465 W 19981002
US 2002013460 A1 20020131 US 2001-852850 20010511
JP 1997-284290 A 19971002
WO 1998-JP4465 W 19981002
US 2000-509778 A320000331

OS MARPAT 130:311813

IT **223542-46-9P 223542-47-0P 223551-31-3P**
223551-33-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of piperazinylisoquinolines and analogs as serotonin antagonists)

RN 223542-46-9 CAPLUS

CN Isoquinoline, 1-(4-ethyl-1-piperazinyl)-3-[(2-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

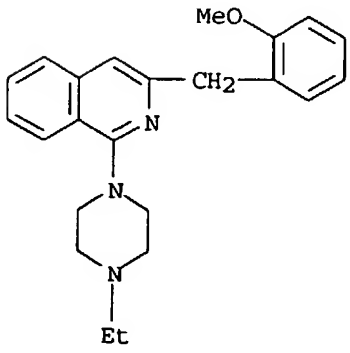


RN 223542-47-0 CAPLUS

CN Isoquinoline, 1-(4-ethyl-1-piperazinyl)-3-[(2-methoxyphenyl)methyl]-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

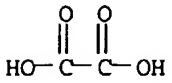
CM 1

CRN 223542-46-9
CMF C23 H27 N3 O

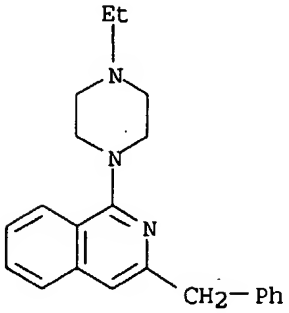


CM 2

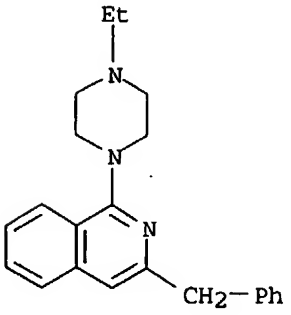
CRN 144-62-7
CMF C2 H2 O4



RN 223551-31-3 CAPLUS
CN Isoquinoline, 1-(4-ethyl-1-piperazinyl)-3-(phenylmethyl)- (9CI) (CA INDEX NAME)

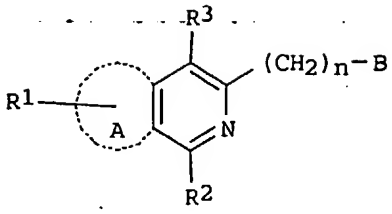


RN 223551-33-5 CAPLUS
CN Isoquinoline, 1-(4-ethyl-1-piperazinyl)-3-(phenylmethyl)-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

GI



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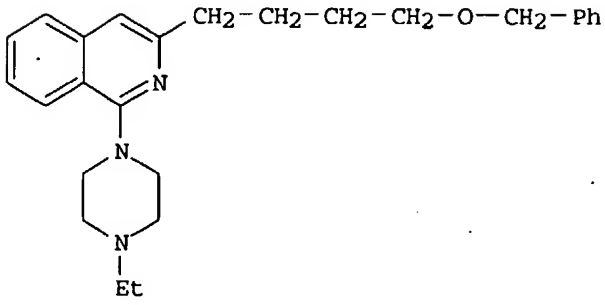
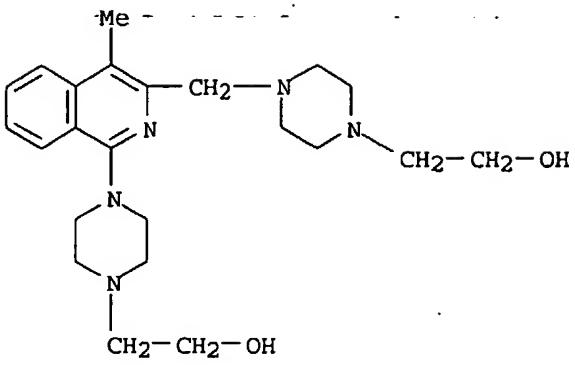


II

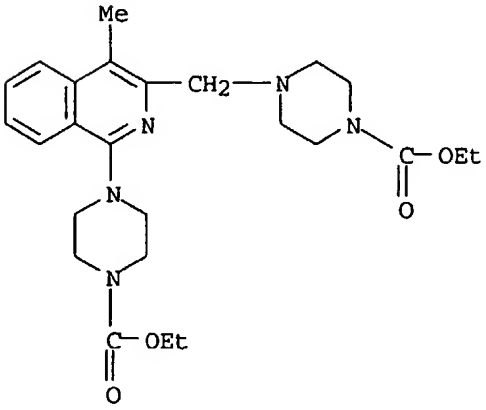
AB The title compds. I [ring A = benzene, pyridine, thiophene or furan ring; B = (un)substituted aryl, etc.; R1 = H, halo, etc.; R2 = 4-morpholinyl, etc.; R3 = H, halo, etc.; n = 0, or 1 - 6] are prepd. I are central muscle relaxing drugs for treating, ameliorating or preventing spastic paralysis or ameliorating myotonia. In an in vitro test for 5HT1 receptor antagonism, the title compd. II showed the Ki value of 21.2 nM.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

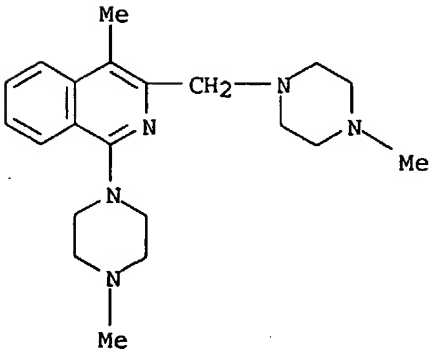
L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1972:564414 CAPLUS
DN 77:164414
TI Reactions of 1-chloro-3-chloromethyl-4-methylisoquinoline
AU Nair, M. D.
CS Ciba Res. Cent., Bombay, India
SO Indian Journal of Chemistry (1972), 10(4), 337-40
CODEN: IJOCAP; ISSN: 0019-5103
DT Journal
LA English
IT **14576-16-0P 14576-17-1P 14577-67-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 14576-16-0 CAPLUS
CN 1-Piperazineethanol, 4-[[1-[4-(2-hydroxyethyl)-1-piperazinyl]-4-methyl-3-isoquinolinyl]methyl]- (9CI) (CA INDEX NAME)



RN 14576-17-1 CAPLUS
CN 1-Piperazinecarboxylic acid, 4-[[1-[4-(ethoxycarbonyl)-1-piperazinyl]-4-methyl-3-isoquinolinyl]methyl]-, ethyl ester (9CI) (CA INDEX NAME)



RN 14577-67-4 CAPLUS
CN Isoquinoline, 4-methyl-1-(4-methyl-1-piperazinyl)-3-[(4-methyl-1-piperazinyl)methyl]- (8CI, 9CI) (CA INDEX NAME)



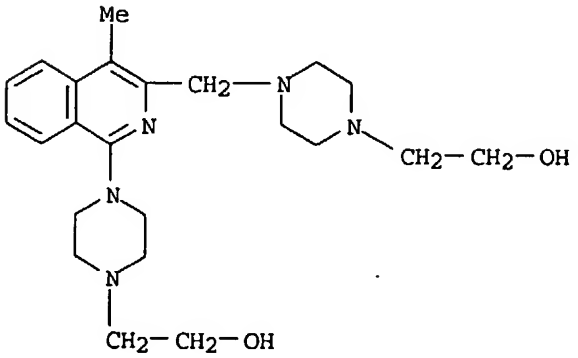
GI For diagram(s), see printed CA Issue.

AB With secondary bases 1-chloro-3-(chloromethyl)-4-methylisoquinoline (I) gave mono or disubstitution products in which the Cl in positions 1 or 3, or both was replaced. In 1-chloro-3-[(2-methylpiperidino)-methyl]-4-methylisoquinoline there was NMR evidence for non-equivalence of benzylic methylene protons from the asymmetry of the 2-Me substituent on piperidine. Reaction of I with piper-azine gave a bis condensation product, II, with NH3 and 4-(.gamma.-aminopropyl)morpholine III and IV were obtained, resp. Nitra-tion of I gave the corresponding 5-NO2 deriv., reaction of which with bases gave mono or disubstituted products, depending on reaction conditions.

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1968:435972 CAPLUS
DN 69:35972
TI 4-Methylisoquinolines
IN Aebi, Albert; Nair, Mohan D.; Bucher, Karl
PA CIBA Ltd.
SO Patentschrift (Switz.), 6 pp.
CODEN: SWXXAS
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CH 438308		19671215	CH	19630221

IT **14576-16-0P 14576-17-1P 14577-67-4P 14825-52-6P 18704-43-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 14576-16-0 CAPLUS
CN 1-Piperazineethanol, 4-[[1-[4-(2-hydroxyethyl)-1-piperazinyl]-4-methyl-3-isoquinolinyl]methyl]- (9CI) (CA INDEX NAME)

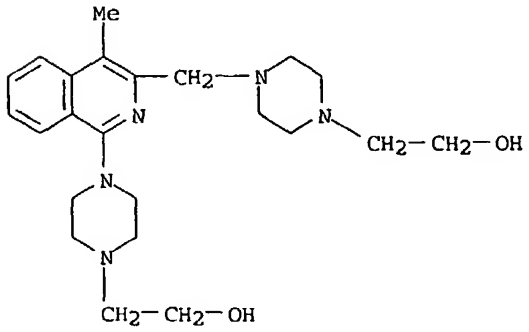


RN 14576-17-1 CAPLUS
CN 1-Piperazinecarboxylic acid, 4-[[1-[4-(ethoxycarbonyl)-1-piperazinyl]-4-methyl-3-isoquinolinyl]methyl]-, ethyl ester (9CI) (CA INDEX NAME)

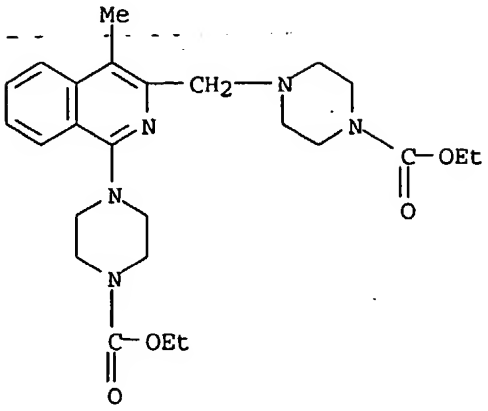
L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1968:435972 CAPLUS
DN 69:35972
TI 4-Methylisoquinolines
IN Aebi, Albert; Nair, Mohan D.; Bucher, Karl
PA CIBA Ltd.
SO Patentschrift (Switz.), 6 pp.
CODEN: SWXXAS
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CH 438308		19671215	CH	19630221

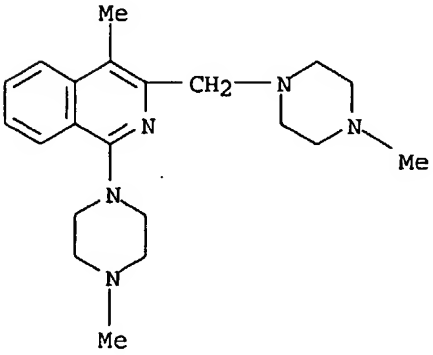
IT **14576-16-0P 14576-17-1P 14577-67-4P**
14825-52-6P 18704-43-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 14576-16-0 CAPLUS
CN 1-Piperazineethanol, 4-[[1-[4-(2-hydroxyethyl)-1-piperazinyl]-4-methyl-3-isoquinolinyl]methyl]- (9CI) (CA INDEX NAME)



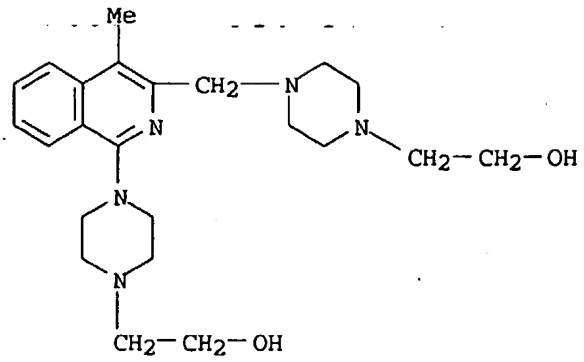
RN 14576-17-1 CAPLUS
CN 1-Piperazinecarboxylic acid, 4-[[1-[4-(ethoxycarbonyl)-1-piperazinyl]-4-methyl-3-isoquinolinyl]methyl]-, ethyl ester (9CI) (CA INDEX NAME)



RN 14577-67-4 CAPLUS
CN Isoquinoline, 4-methyl-1-(4-methyl-1-piperazinyl)-3-[(4-methyl-1-piperazinyl)methyl]- (8CI, 9CI) (CA INDEX NAME)

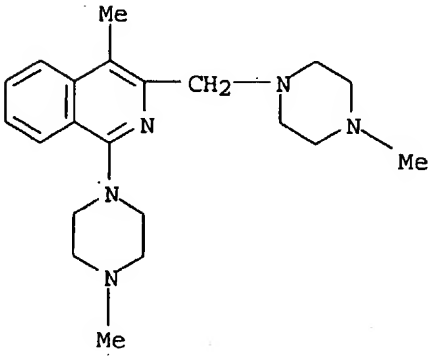


RN 14825-52-6 CAPLUS
CN 1-Piperazineethanol, 4,4'-[methylene(4-methyl-3,1-isoquinolinediyl)]di-, hydrochloride (8CI) (CA INDEX NAME)



● x HCl

RN 18704-43-3 CAPLUS
CN Isoquinoline, 4-methyl-1-(4-methyl-1-piperazinyl)-3-[(4-methyl-1-piperazinyl)methyl]-, monohydrochloride (8CI) (CA INDEX NAME)



● HCl

GI For diagram(s), see printed CA Issue.

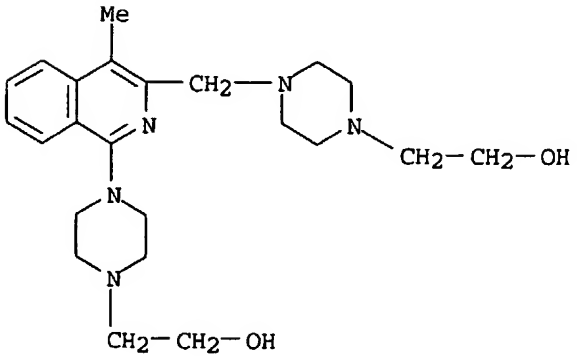
AB The title compds. are prepd. by treating 1-chloro-3-chloromethyl-4-methylisoquinoline (I) or its substituted derivs. with secondary amines. Thus, 1.55 g. I and 5 ml. morpholine was heated overnight in a pressure vessel at 150.degree.. The cryst. suspension was then evapd. to dryness, taken up in CHCl3, extd. 2 times with dil. aq. HCl, and the aq. exts. adjusted to pH 8-9 with NaOH. The oil which sepd. gradually crystd., and was sepd. and recrystd. from iso-PrOH to give II (R = H and R1 = morpholino), m. 100.degree.; dihydrochloride m. 229-32.degree. (decompn.) and maleate m. 173-5.degree.. Other II similarly prepd. are shown in the table. The starting material for II (R = NO2) was prepd. by treating I with concd. H2SO4 and fuming HNO3 to give II (R = NO2, R1 = Cl), m. 104-5.degree.. A mixt. of 4 g. 1,7-dichloro-3-chloromethyl-4-methylisoquinoline (IV) and 50 ml. morpholine was refluxed 4 hrs., and excess morpholine was then removed under reduced pressure. [TABLE

OMITTED] The residue was treated with aq. Na2CO3 until alk. and extd. with CHCl3. The exts. were evapd. to give 7-chloro-4-methyl-1-morpholino-3-(morpholinomethyl)isoquinoline, which was purified by conversion to its maleate and then to the free base, m. 120.degree. (EtOH). IV was prepd. by treating 4,4-dimethylhomophthalimide with fuming HNO3 and concd. H2SO4 at -10.degree. to give 4,4-dimethyl-7-nitrohomophthalimide, m. 209-11.degree.. Hydrogenation over Pd-C gave the 7-amino compd., m. 176-9.degree., which was diazotized and treated with CuCl to give the 7-chloro deriv., m. 200.degree.. Treatment with POCl3 gave IV, m. 135.degree.. These compds. are used in pharmaceutical applications.

L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1967:421848 CAPLUS
DN 67:21848
TI New antitussive isoquinoline derivatives
PA CIBA Ltd.
SO Fr. M., 10 pp.
CODEN: FMXXAJ
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI FR 3782		19660131		
			CH	19630121
			CH	19640121

IT **14576-16-0P 14576-17-1P 14577-67-4P**
14601-04-8P 14825-52-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 14576-16-0 CAPLUS
CN 1-Piperazineethanol, 4-[[1-[4-(2-hydroxyethyl)-1-piperazinyl]-4-methyl-3-isoquinolinyl]methyl]- (9CI) (CA INDEX NAME)



RN 14576-17-1 CAPLUS
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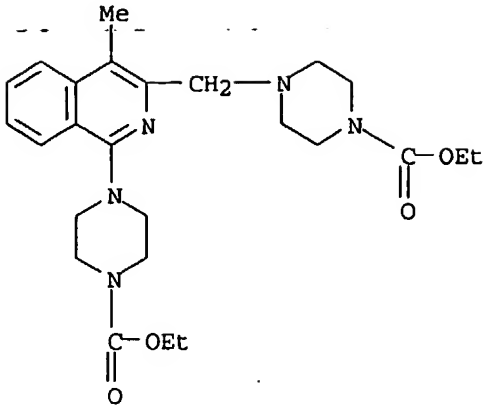
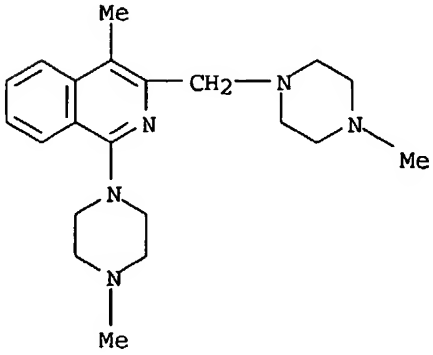
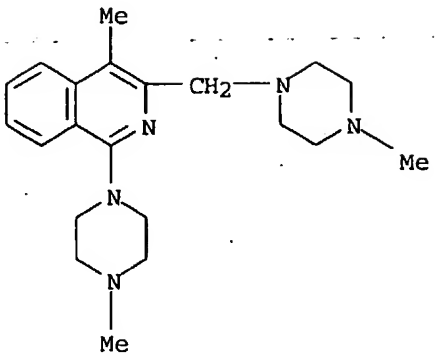


RN 14577-67-4 CAPLUS
CN Isoquinoline, 4-methyl-1-(4-methyl-1-piperazinyl)-3-[(4-methyl-1-piperazinyl)methyl]- (8CI, 9CI) (CA INDEX NAME)

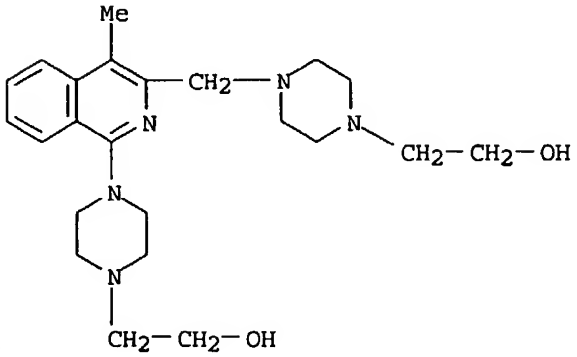


RN 14601-04-8 CAPLUS
CN Isoquinoline, 4-methyl-1-(4-methyl-1-piperazinyl)-3-[(4-methyl-1-piperazinyl)methyl]-, hydrochloride (8CI) (CA INDEX NAME)



●x HCl

RN 14825-52-6 CAPLUS
CN 1-Piperazineethanol, 4,4'-[methylene(4-methyl-3,1-isoquinolinediyl)]di-, hydrochloride (8CI) (CA INDEX NAME)



●x HCl

GI For diagram(s), see printed CA Issue.

AB New antitussive isoquinoline derivs. with general formula (I) are prepd. A mixt. of 9 g. 1-chloro-3-chloromethyl-4-methylisoquinoline (II) and 40 cc. piperidine (III) is heated in a sealed tube 8 hrs. at 150.degree., the reaction mixt. concd. in vacuo, treated with water, and extd. with CH2Cl2, the ext. dried and evapd. to dryness, and the residue in CHCl3 passed through activated alumina to give 4-methyl-1-piperidino-3-piperidinomethylisoquinoline, m. 111.degree. (water-EtOH). The following products are prepd. in a similar way (starting materials, reaction time, reaction temp., final product, m.p., derivs., and m.p. given): II (9 g.), pyrrolidine (40 cc.), 8 hrs., 150.degree., 4-methyl-1-(1-pyrrolidinyl)-3-(1-pyrrolidinylmethyl)isoquinoline, -, hydrochloride, 239.degree.; II (8 g.), N-methylpiperazine (IV) (50 cc.), 8 hrs., 150.degree., 4-methyl-1-(N'-methylpiperazino)-3-(N'-methylpiperazinomethyl)isoquinoline, 110-11.degree., hydrochloride, 238.degree.; II (8 g.),

N-(.beta.-hydroxyethyl)piperazine (40 cc.), 8 hrs., 150.degree., 4-methyl-1-[N'-(.beta.-hydroxyethyl)piperazino]-3-[N'-(.beta.-hydroxyethyl)piperazinomethyl]isoquinoline, 112.degree., hydrochloride, 262.degree. (decompn.); II (6 g.), Et2NH (15 cc.), 8 hrs., 150.degree., 4-methyl-1-diethylamino-3-diethylaminomethylisoquinoline, -, dimaleate, 109-11.degree.; II (4.5 g.), ethanolamine (15 cc.), 3 hrs., 130.degree., 4-methyl-1-(.beta.-hydroxyethylamino)-3-(.beta.-hydroxyethylaminomethyl)isoquinoline, -, hydrochloride, 252-4.degree.; II (5 g.), N-carbethoxypiperazine (V) (20 cc.), 6 hrs., 140.degree., 4-methyl-1-(N'-carbethoxypiperazino)-3-(N'-carbethoxypiperazinomethyl)isoquinoline, 90-2.degree., -, -; II (5 g.), 2-methylpiperidine (20 cc.), 6 hrs., 140.degree., 1-chloro-4-methyl-3-(2-methylpiperidinomethyl)isoquinoline (VI), 106-8.degree., -, -; VI (6 g.), morpholine (VII) (20 cc.), 14 hrs., 170.degree., 4-methyl-1-morpholino-3-(2-methylpiperidinomethyl)isoquinoline, 103-4.degree., -, -; 1-chloro-3-chloromethyl-4-methyl-5-nitroisoquinoline (VIII) (2 g.), VII (10 cc.), 2 hrs., 120.degree., 4-methyl-1-morpholino-3-morpholinomethyl-5-nitroisoquinoline (IX), 145-6.degree., -, -; VIII (2.5 g.), III (10 cc.), 2.5 hrs., 80.degree., 4-methyl-5-nitro-1-piperidino-3-piperidinomethylisoquinoline, 104-6.degree., -, -; VIII (2.5 g.), p-anisidine (4.55 g.), EtOH (80 cc.), 4 hrs., reflux, 1-p-anisidino-3-p-anisidinomethyl-4-methyl-5-nitroisoquinoline, 183-5.degree., -, -; 1,7-dichloro-3-chloromethyl-4-methylisoquinoline (X) (4 g.), VII (50 cc.), 4 hrs., reflux, 7-chloro-4-methyl-1-morpholino-3-morpholinomethylisoquinoline, 120.degree., maleate, -; VIII (5 g.), III (8 cc.), EtOH (75 cc.), 1 hr., reflux, 1-chloro-4-methyl-5-nitro-3-piperidinomethylisoquinoline, 67-79.degree., -, -; II (4.5 g.), III (15 cc.), 2 hrs., 80.degree., 1-chloro-4-methyl-3-piperidinomethylisoquinoline, 79-80.degree., -, -; VIII (3.5 g.), IV (2.58 g.), EtOH (100 cc.), 2 hrs., reflux, 1-chloro-3-(N'-methylpiperazinomethyl)-4-methyl-5-nitroisoquinoline, 173-5.degree., -, -; VIII (4 g.), V (10 cc.), EtOH (75 cc.), 1 hr., reflux, 1-chloro-3-(N'-carbethoxypiperazinomethyl)-4-methyl-5-nitroisoquinoline, 127-8.degree., -, -; VIII (2.71 g.), diethanolamine (4.5 g.), dioxane (50 cc.), 3 hrs., reflux, 1-chloro-3-[bis(.beta.-hydroxyethyl)aminomethyl]-4-methyl-5-nitroisoquinoline, 110-12.degree., -, -; II (5.0 g.), 4-methylpiperidine (5.5 cc.), 2 hrs., 80.degree., 1-chloro-3-(4-methylpiperidinomethyl)-4-methylisoquinoline, 83-5.degree., -, -; II (5.0 g.), concd. aq. NH3 (80 cc.), hydrated CuSO4 (1.0 g.), 30 hrs., 140.degree., bis(1-chloro-4-methyl-3-isoquinolylmethyl)amine, 131-2.degree., -, -; II (5.0 g.), N-(.gamma.-aminopropyl)morpholine (6.5 g.), 2 hrs., 100.degree., N,N-bis(1-chloro-4-methyl-3-isoquinolylmethyl)-N-(.gamma.-morpholinopropyl)amine, 110-12.degree., -, -. Some starting materials and other products are prepd. as follows: II (6 g.) is added slowly with stirring to a cooled mixt. of 15 cc. concd. H2SO4 and 15 cc. fuming HNO3 and the mixt. stirred 1.5 hrs. below 5.degree. and poured over a mixt. of ice and water to ppt. VIII, m 104-5.degree. (EtOH). A mixt. of 4 g. IX, 0.3 g. Pd-C and 150 cc. 95% EtOH is hydrogenated 1.5 hrs. to give 5-amino-4-methyl-1-morpholino-3-morpholinomethylisoquinoline (XI), m. 134-5.degree. (EtOH). A soln. of 1.6 g. NaNO2 in 5 cc. water is added slowly to a cooled soln. of 8 g. XI in 6 cc. concd. HCl and 6 cc. water, the resulting soln. poured into a cooled soln. of Cu2Cl2 (prepd. from 8 g. CuSO4) and then is heated at 60.degree., and the ppt. suspended in 25 cc. water, alkalinized, and extd. with CHCl3 to give 5-chloro-4-methyl-1-morpholino-3-morpholinomethylisoquinoline, m. 104.degree.. 4,4-Dimethylhomophthalimide (15 g.) is added slowly with stirring to a cooled (-10.degree.) mixt. of 30 cc. concd. H2SO4 and 30 cc. fuming HNO3 and the mixt. stirred 1 hr. below 20.degree. and poured over a mixt. of ice and

water to ppt. 4,4-dimethyl-7-nitrohomophthalimide (XII), m. 209-11.degree. (EtOH). A mixt. of 23.4 g. XII, 0.5 g. Pd-C, and 200 cc. MeOH is hydrogenated at 50.degree./3.4 atm. .apprx.1.5 hrs. to give 4,4-dimethyl-7-aminohomophthalimide (XIII), m. 176-9.degree. (MeOH). Concd. H_2SO_4 (26 g.) is added slowly to a mixt. of 20 g. XIII and 90 cc. water, and cooled at 0.degree., 8.4 g. $NaNO_2$ in 24 cc. water added slowly to it, and this mixt. is added slowly to a soln. of Cu_2Cl_2 (prepd. from 33.4 g. $CuSO_4$), and the mixt. heated at 60.degree. 30 min., cooled, dild. with water, and extd. with $CHCl_3$ to give 4,4-dimethyl-7-chlorohomophthalimide (XIV), m. 200.degree. (EtOH). A mixt. of 10 g. XIV, 0.5 cc. water, and 40 cc. $POCl_3$ is heated in a sealed tube at 200.degree. 5 hrs. to give X, m. 135.degree. (hexane-$CHCl_3$). Some recipes for the prepn. of pharmacol. compns. are also given.

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